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A Phase IIb, Multicenter, Open-Label, Safety, and Efficacy Study of High-Dose, Propylene Glycol-Free Melphalan Hydrochloride for Injection (EVOMELA) for Myeloablative Conditioning in Multiple Myeloma Patients Undergoing Autologous Transplantation

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A B S T R A C T

Autologous stem cell transplantation (ASCT) after high-dose melphalan conditioning is considered a standard of care procedure for patients with multiple myeloma (MM). Current formulations of melphalan (eg, Alkeran for Injection [melphalan hydrochloride]; GlaxoSmithKline, Research Triangle Park, NC, USA) have marginal solubility and limited chemical stability upon reconstitution. Alkeran requires the use of propylene glycol as a co-solvent, which itself has been reported to cause such complications as metabolic/renal dysfunction and arrhythmias. EVOMELA (propylene glycol-free melphalan HCl; Spectrum Pharmaceuticals, Inc., Irvine, CA, USA) is a new i.v. melphalan formulation that incorporates Captisol (Ligand Pharmaceuticals, Inc., La Jolla, CA, USA), a specially modified cyclodextrin that improves the solubility and stability of melphalan and eliminates the need for propylene glycol. This new formulation has been shown to be bioequivalent to Alkeran. EVOMELA (200 mg/m^2) was administered as 2 doses of 100 mg/m^2 each in a phase IIb, open-label, multicenter study to confirm its safety and efficacy as a high-dose conditioning regimen for patients with MM undergoing ASCT. At 5 centers, 61 patients (26 women) with a median age of 62 years (range, 32-73) were enrolled. All patients achieved myeloablation with a median time of 5 days post-ASCT, and all successfully achieved neutrophil and platelet engraftment with median times of 12 days post-ASCT and 13 days post-ASCT, respectively; treatment-related mortality on day 100 was 0%. Overall response rate (according to independent, blinded review) was high (100%), with an overall complete response rate of 21% (13% stringent complete response; 8% complete response) and overall partial response rate of 79% (61% very good partial response; 18% partial response). The incidence of grade 3 mucositis and stomatitis was low (10% and 5%, respectively) with no grade 4 mucositis or stomatitis reported (graded according to National Cancer Institute Common Terminology Criteria for Adverse Events). Based on investigators' assessment of mucositis using the World Health Organization (WHO) oral toxicity scale, 75% of patients had a shift in mucositis score from WHO grade 0 at baseline to a higher grade on study, of which 13% of patients reported WHO grade 3 as the worst post-treatment mucositis over the course of the study; there were no reports of WHO grade 4 mucositis during the study. This study confirms the efficacy and acceptable safety profile of EVOMELA, a new propylene glycol-free melphalan formulation, as a high-dose conditioning regimen for ASCT in patients with MM.

INTRODUCTION

Myeloablative conditioning with high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) is considered to be the standard of care treatment for

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symptomatic, transplant-eligible patients with multiple myeloma (MM) [1-3]. The most commonly used conditioning regimen in this setting is i.v. administration of high-dose melphalan [4-6]. Multiple studies have also confirmed the efficacy of melphalan over other myeloablative therapies [7-10]. Conventional melphalan formulations (eg, Alkeran; GlaxoSmithKline, Research Triangle Park, NC, USA) have marginal solubility, limited chemical stability after reconstitution (necessitating completed administration within 1 hour), and require the use of propylene glycol as a co-solvent [11]. Propylene glycol can potentially contribute to an array of side effects, including metabolic/renal dysfunction and arrhythmias [12]. Thus, conventional melphalan formulations, when administered at the high doses used for myeloablative conditioning, can put patients at risk of these potential propylene glycol–associated toxicities.

Propylene glycol-free melphalan hydrochloride (EVOMELA; Spectrum Pharmaceuticals, Inc., Irvine, CA, USA) is a new formulation of melphalan that incorporates Captisol (Ligand Pharmaceuticals, Inc., La Jolla, CA, USA), a specially modified cyclodextrin that improves the solubility and stability of melphalan [13,14]. This new formulation eliminates the risk of propylene glycol toxicities by using the Captisol technology used in the formulation of 6 other US Food and Drug Administration–approved human parenteral drugs (Vfend, Nexterone, Geodon, Abilify, Kyprolis, and Noxafil) [15-20].

The objective of this study was to confirm the safety and efficacy of high-dose EVOMELA as a myeloablative conditioning regimen in patients with MM undergoing ASCT. Propylene glycol-free melphalan HCl has been previously shown to be bioequivalent to Alkeran in a phase IIa study [14].

METHODS

Patients and Procedures

This phase IIb, open-label, nonrandomized study was conducted at 5 centers in the United States. The primary aim was to confirm the safety and efficacy of high-dose EVOMELA as a myeloablative conditioning regimen in patients who had symptomatic MM and qualified for ASCT. Patients enrolled in the study received 200 mg/m^2 of i.v. melphalan as 2 doses of EVOMELA (100 mg/m^2 each, infusion time of approximately 30 minutes) on days −3 and −2 followed by a day of rest before ASCT was performed on day 0 (Figure 1). The decision to dose melphalan over 2 days was based on the regimen used in the previously conducted phase IIa study in which propylene glycol-free melphalan HCl was shown to be bioequivalent to Alkeran; prior prospective studies have used the 2-day dosing regimen and authorities in the field consider both dosing regimens to be equivalent [14,21,22].

Key inclusion criteria included patients with symptomatic MM who had adequate cardiac, hepatic, renal, and pulmonary function; an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; and an adequate autologous stem cell collection available (≥2 × 10^6 CD34$^+$ cells/kg). Treatment-related mortality (TRM), adverse events, overall response rate (ORR), myeloablation, neutrophil engraftment, and platelet engraftment were assessed by site investigators as defined below. MM response rates were initially assessed by the site investigator using the International Myeloma Working Group (IMWG) uniform response criteria for evaluating MM response and were also adjudicated by an independent, blinded reviewer to ensure consistency across sites.

Myeloablation, neutrophil engraftment, and platelet engraftment were assessed from daily complete blood counts with differentials conducted until the time of neutrophil and platelet engraftment. Bone marrow aspirates/biopsies were obtained before study treatment and on day +100 after ASCT to further assess disease status. Safety was assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. Mucositis was also assessed using the World Health Organization (WHO) oral toxicity scale. Agents to treat symptoms of mucositis (oral narcotics, oral mouthwashes, nondrug cryotherapy, etc.) were allowed during the study as per institutional protocols.

All patients were informed of the investigational nature of the study; all signed and were given a copy of written informed consent in accordance with institutional and federal guidelines. This study was approved by the institutional review board at each participating site and was registered on ClinicalTrials.gov (identification number: NCT01660633).

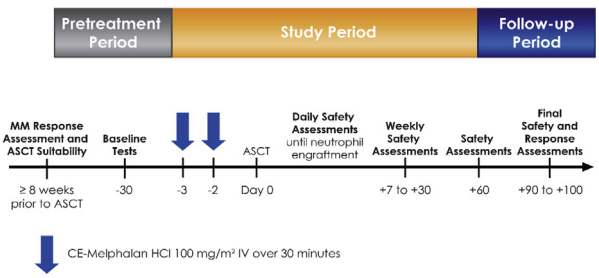

Figure 1. Study schema. Patients enrolled in the study received 200 mg/m^2 of i.v. melphalan as 2 doses of EVOMELA (100 mg/m^2 each) on days −3 and −2 followed by a day of rest before ASCT was performed on day 0. Patients were evaluated for safety and response through day +100. CE indicates Captisol-enabled.

Statistical Analyses

MM response rates according to each category of response (stringent complete response [sCR], complete response [CR], very good partial response [VGPR], partial response [PR], stable disease, and progressive disease) were summarized by the proportion of patients meeting each criterion along with Clopper-Pearson 95% confidence intervals (CI). The Kaplan-Meier methodology was used to summarize time-to-event variables (time to myeloablation, time to neutrophil engraftment, and time to platelet engraftment) along with 95% CIs. The rates of myeloablation, engraftment (neutrophil and platelets), and nonengraftment in the study population were determined using the definitions below and were summarized by the proportions of patients meeting each criterion.

Adverse event coding was performed using the *Medical Dictionary for Regulatory Activities* version 13.1, and the severity of the toxicities was graded according to NCI CTCAE version 4.03 whenever possible. Adverse events were summarized by severity and by causality (related and not related to study treatment) as assessed by the investigators. Clinically relevant laboratory abnormalities (ie, those that met grade 3 or 4 criteria according to NCI CTCAE) were summarized. The incidence of oral mucositis was also summarized by WHO grade. Time from the start of the first dose of study medication to peak oral mucositis score was calculated and was summarized using Kaplan-Meier estimates.

Definitions

TRM was defined as death without relapse or progression during the first 100 days after ASCT. ORR was defined as greater than or equal to a PR by IMWG criteria on day +100 after ASCT. Neutrophil engraftment was defined as an absolute neutrophil count > .5 × 10^9/L for 3 consecutive daily assessments. Platelet engraftment was defined as an untransfused platelet measurement > 20,000/mm^3 for 3 consecutive daily assessments. Serious adverse events (SAEs) were defined as adverse events that resulted in death, were life-threatening, required hospitalization, resulted in persistent or significant disability/incapacity, resulted in a congenital anomaly/birth defect, or were considered serious based on medical judgment. Treatment-emergent adverse events (TEAE) were defined as adverse events that occurred or worsened on or after first study treatment up through 30 days after last study treatment and/or any treatment-related adverse events regardless of the onset date. High-risk cytogenetics were defined as t(4;14), t(14;16), t(14;20), del17p, hypodiploidy, or chromosome 1 abnormalities.

RESULTS

Study Population

A total of 76 patients was screened, and 61 patients were enrolled. The study population consisted of 35 men (57%) and 26 women (43%) with a median patient age of 62 years (range, 32 to 73). Most patients (80%) were white, and 18% of patients were African American. Most patients (59%) had an ECOG performance status of 0. Cytogenetics were classified as high risk in 15% of patients and standard risk in 48% of patients; 36% of patients had missing cytogenetic information. Five patients (8%) had relapsed disease, and 56 patients (92%) were newly diagnosed MM receiving upfront ASCT. Overall, 53 patients (87%) had 1 prior therapy, 5 patients (8%) had 2 prior therapies, and 3 patients (5%) had 3 or more prior

therapies; 5 patients (8%) had relapsed after a prior ASCT. Based on the site investigator's response assessment, pretreatment (before ASCT) disease status greater than or equal to PR was 79%. On independent reviewer's response assessment, pretreatment (before ASCT) disease status greater than or equal to PR was 82%. Table 1 summarizes patient characteristics.

Efficacy Results

Efficacy was determined based on clinical response (MM responses at day +100 using the IMWG uniform response criteria) and by determining the rates and timing of myeloablation and engraftments. Clinical response assessments from both the site investigator and blinded independent reviewer are presented and discussed.

Clinical response

All patients were assessable for response. Based on the site investigator's assessments after EVOMELA and ASCT at day +100, ORR was 95% (Table 2, Figure 2). The CR rate was 31%, with 16% sCR and 15% CR; the PR rate was 64%, with 43% VGPR and 21% PR by day +100. Based on the independent reviewer's response assessment following EVOMELA and ASCT at day +100, the ORR was 100% (Table 2, Figure 2). The CR rate was 21%, with 13% sCR and 8% CR; the PR rate was 79%, with 61% VGPR and 18% PR by day +100. In addition, the 5 patients in this study who had relapsed after a prior ASCT were shown to achieve a response to subsequent treatment with EVOMELA with 1 sCR, 2 CRs, 1 VGPR, and 1 PR based on the independent reviewer assessment.

Table 1
Patient Characteristics (N = 61)

Characteristic	Value
Median age, yr (range)	62 (32-73)
Gender	
Male	35 (57%)
Female	26 (43%)
Race	
White	49 (80%)
Black/African American	11 (18%)
Other	1 (2%)
International staging system stage at diagnosis*	
I	28 (47%)
II	16 (27%)
III	15 (25%)
ECOG performance score at transplant	
0	36 (59%)
1	23 (38%)
2	2 (3%)
Cytogenetics	
High risk†	9 (15%)
Standard risk	29 (48%)
Missing	23 (37%)
Prior lines of treatment‡	
1	53 (87%)
2	5 (8%)
≥3	3 (5%)
Relapsed disease	5 (8%)
Prior ASCT	5 (8%)
Pretreatment (before ASCT) response (independent reviewer assessment)	
Overall response (sCR, CR, VGPR, or PR)	50 (82%)
sCR	0 (0%)
CR	3 (5%)
VGPR	27 (44%)
PR	20 (33%)
Stable disease	8 (13%)
Progressive disease	3 (5%)
Pretreatment (before ASCT) response (investigator assessment)	
Overall response (sCR, CR, VGPR, or PR)	48 (79%)
sCR	0 (0%)
CR	6 (10%)
VGPR	22 (36%)
PR	20 (33%)
Stable disease	8 (13%)
Progressive disease	5 (8%)

* A total of 59 patients had International Staging System stage available.
† Defined as t(4;14), t(14;16), t(14;20), del17p, hypodiploidy, or chromosome 1 abnormalities.
‡ Induction therapy before ASCT included as a prior line of treatment.

Table 2
Summary of MM Response (N = 61)

Time Point	MM Response Assessment	Value
Independent Reviewer Assessment		
Response at day +100 after ASCT	Overall response (sCR, CR, VGPR, or PR)	61 (100%)
	sCR	8 (13%)
	CR	5 (8%)
	VGPR	37 (61%)
	PR	11 (18%)
	Stable disease	0 (0%)
	Progressive disease	0 (0%)
Investigator Assessment		
Response at day +100 after ASCT	Overall response (sCR, CR, VGPR, or PR)	58 (95%)
	sCR	10 (16%)
	CR	9 (15%)
	VGPR	26 (43%)
	PR	13 (21%)
	Stable disease	2 (3%)
	Progressive disease	1 (2%)

Myeloablation, neutrophil engraftment, and platelet engraftment

All patients achieved myeloablation with a median time of 5 days post-ASCT (range, −1 to 6). All patients successfully achieved neutrophil and platelet engraftment with median times of 12 days post-ASCT (range, 10 to 16) and 13 days post-ASCT (range, 10 to 28), respectively.

Safety Results

All 61 patients in the study received 2 doses of EVOMELA at 100 mg/m^2 each on days −3 and −2 for a total dose of 200 mg/m^2. The duration of infusion of the melphalan doses varied between 24 and 48 minutes, with a mean infusion time of 32.8 minutes. No TEAEs led to discontinuation from the study.

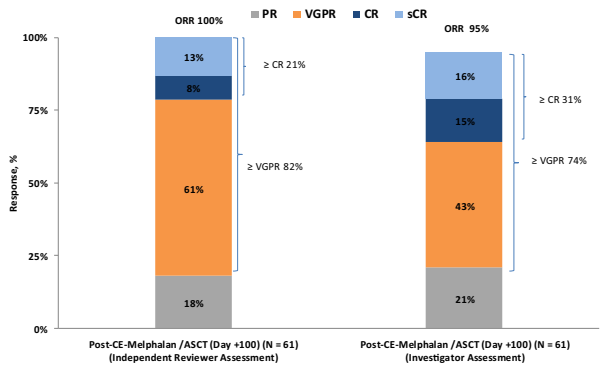

Figure 2. MM response rates were assessed by an independent reviewer (left) and by the site investigator (right) using the IMWG uniform response criteria for evaluating MM response.

Treatment-related mortality

There were no deaths on study; thus, TRM was 0%.

Hematologic TEAEs

All patients (100%) had at least 1 grade 4 hematologic TEAE indicative of myeloablation. Grades 3 to 4 hematologic TEAEs are presented in Table 3.

Nonhematologic TEAEs

All patients (100%) had at least 1 nonhematologic TEAE. Nonhematologic TEAEs that were reported in ≥25% of patients are presented in Table 4. Nonhematologic TEAEs were reported as grade 3 in 69% of patients and grade 4 in 10% of patients. Grade 3 nonhematologic TEAEs reported in ≥5% of patients were hypophosphatemia (41%), hypokalemia (26%), mucosal inflammation (10%), hyperglycemia (8%), stomatitis (5%), hypocalcemia (5%), and hypertension (5%). Grade 4 nonhematologic TEAEs included hypophosphatemia (4 patients), sepsis (2 patients), hematochezia (1 patient), and hypokalemia (1 patient). Notably, the incidence of grade 3 mucositis and grade 3 stomatitis was low (10% and 5%, respectively), and no grade 4 mucositis or grade 4 stomatitis was reported. All grades 3 and 4 TEAEs resolved over the course of the study.

Serious adverse events

Twelve patients (20%) experienced treatment-emergent SAEs while on study, and all SAEs resolved. Ten of the treatment-emergent SAEs were considered at least possibly related to study treatment, and the remaining 8 were considered unlikely or not related to study treatment. Treatment-emergent SAEs included pyrexia (5 patients, 8%); febrile neutropenia, hematochezia, and acute renal failure (2 patients each, 3%); and atrial fibrillation, cellulitis, dehydration, mucosal inflammation, oral pain, presyncope, and staphylococcal infection (1 patient each, 2%). Most treatment-emergent SAEs were grade 3 and included 2 events each of pyrexia and acute renal failure and 1 event each of mucosal inflammation, hematochezia, oral pain, febrile neutropenia, cellulitis, staphylococcal infection, atrial fibrillation, dehydration, and presyncope. One treatment-emergent SAE (hematochezia) was grade 4. These treatment-emergent SAEs are commonly reported events noted during myeloablative therapy [23-25].

Oral mucositis

Based on investigators' assessment using the WHO oral toxicity scale, 46 patients (75%) had a shift in mucositis score from grade 0 at baseline to a higher grade on study, of which 8 patients (13%) reported grade 3 as the worst post-treatment mucositis over the course of the study. There were no reports of grade 4 mucositis during the study (Table 5).

Table 3
Summary of Hematologic TEAEs by Worst Grade

Adverse Event	Grade 3	Grade 4	All*
All hematologic adverse events†	61 (100)	61 (100)	61 (100)
Neutropenia/neutrophil count decreased	3 (5)	58 (95)	61 (100)
Leukopenia/WBC count decreased	1 (2)	60 (98)	61 (100)
Lymphopenia/lymphocyte count decreased	0 (0)	60 (98)	60 (98)
Thrombocytopenia/platelet count decreased	0 (0)	60 (98)	60 (98)
Anemia	31 (51)	0 (0)	40 (66)
Febrile neutropenia	17 (28)	0 (0)	25 (41)

Values are number of cases with percents in parentheses.

* All adverse events indicative of myeloablation regardless of worst toxicity.

† Patients were counted only once across the combined preferred terms by worst toxicity.

Table 4
Summary of Nonhematologic TEAEs Experienced by ≥25% of Patients (N = 61)

Adverse Event	No. of Patients (%)
Diarrhea	57 (93)
Nausea	55 (90)
Fatigue	47 (77)
Hypokalemia	45 (74)
Vomiting	39 (64)
Hypophosphatemia	30 (49)
Decreased appetite	30 (49)
Pyrexia	29 (48)
Constipation	29 (48)
Mucosal inflammation	23 (38)
Dizziness	23 (38)
Peripheral edema	20 (33)
Stomatitis	17 (28)
Abdominal pain	17 (28)
Dysgeusia	17 (28)
Dyspepsia	16 (26)

Adverse events of special interest

Adverse events of special interest included atrial fibrillation and acute renal failure. Three patients (5%) had TEAEs of atrial fibrillation: 2 were grade 2 and 1 was grade 3. The grade 3 atrial fibrillation was a treatment-emergent SAE that occurred in a patient with a history of hypercholesterolemia and hypertension that resolved 8 days after the last dose of study medication. For the 2 patients with grade 2 atrial fibrillation, 1 patient had a history of atrial fibrillation, hyperlipidemia, and hypertension, and the other patient had a history of hypercholesterolemia, hypertension, and coronary artery disease. Three patients (5%) had TEAEs of acute renal failure that resolved on follow-up. All events of acute renal failure were considered not to be related to the study medication. Two acute renal failure events were grade 3 treatment-emergent SAEs, and 1 event was a grade 2 TEAE.

DISCUSSION

A previously conducted phase IIa pharmacokinetic crossover study (n = 24) showed the efficacy of propylene glycol-free melphalan HCl given as a high-dose conditioning regimen to patients with MM undergoing ASCT, with all patients achieving myeloablation and subsequent hematologic engraftment; the observed safety profile was consistent with that already established for conventional melphalan formulations [14]. Additionally, this study demonstrated the bioequivalence of propylene glycol-free melphalan HCl to Alkeran for Injection with mean plasma concentration profiles that were nearly superimposable for the 2 melphalan formulations [14]. Geometric mean ratios from a non-compartmental analysis demonstrated model-estimated C_{max}, $AUC_{0-\infty}$, and AUC_{0-t} values of 112.0%, 110.9%, and 110.8%, respectively, with associated 90% CIs within 80.0% to 125.0%.

A phase IIa bioequivalence study directly compared Alkeran with propylene glycol-free melphalan HCl and was designed as a crossover study that administered 1 or the other product on the first day followed by the alternate product on the second day [14]. Therefore, the dosing in the phase IIa study had to be 100 mg/m^2 over 2 days, and the

Table 5
Shift in Mucositis Results

Baseline Mucositis Result	Worst Postbaseline Mucositis Result						
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing	Total
Grade 0	9 (15)	20 (33)	18 (30)	8 (13)	0	0	55 (90)
Grade 1	0	0	0	0	0	0	0
Grade 2	0	0	1 (2)	0	0	0	1 (2)
Grade 3	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0
Missing	4 (7)	1 (2)	0	0	0	0	5 (8)

Values are number of cases with percents in parentheses.

current follow-on phase IIb study used the same dosing regimen for melphalan. Melphalan is commonly administered as 200 mg/m^2 on a single day and less commonly as 100 mg/ m^2 daily on 2 consecutive days as was done in the propylene glycol-free melphalan HCl study. Prior prospective studies in MM have used the 100 mg/m^2 × 2-day dosing, and authorities in the field consider both methods of melphalan administration to be equivalent [21,22]. A comparative study did demonstrate a higher risk of mucositis with the 2-day dosing scheme [26].

All patients in the phase IIb study (n = 61) described here demonstrated myeloma responses, with an ORR of 95% and a CR rate of 31%. The ORR, based on the blinded, independent review, was 100% with an overall CR rate of 21%. The lower incidence of CRs based on the independent review compared with the site review was attributed to missing data, such as 24-hour urine samples from select patients, that did not allow for confirmation of a CR and subsequent response downgrading. In addition, patients in this study who had relapsed from a prior ASCT (n = 5) were shown to achieve a response to salvage ASCT with EVOMELA.

Notably, nonhematologic TEAEs in this study were mostly grade 1 or 2 in severity, and no treatment-related deaths occurred despite enrollment of patients undergoing salvage ASCT (8%) and patients aged 65 or above (30%). The TRM rate reported in recently published studies using comparable i.v. melphalan treatment regimens (200 mg/m^2) and a similar TRM definition, generally ≤3% [23-25].

Gastrointestinal TEAEs, in particular diarrhea, nausea, and vomiting, occurred in >50% of patients in this study and are expected adverse events associated with high-dose melphalan; the rates of these adverse events were consistent with the rates in recently published studies [23-25]. The incidence of WHO grade 3 oral mucositis (which was specifically graded daily by the investigators) was only 13% in the current study, after administration of EVOMELA, with no grade 4 events compared with WHO grade 3 or 4 oral mucositis incidences in the published literature after conventional i.v. melphalan formulations of 46% [27]. The WHO scale for rating mucositis is generally considered a more specific and sensitive measure of mucositis than from general adverse event reporting. The incidence of grade 3 or 4 mucositis, reported as adverse events of mucosal inflammation and stomatitis using the NCI CTCAE scale, was also lower in this study (15%) than rates generally reported in the published literature with conventional i.v. melphalan (12% to 43%) [28,29]. However, it should be noted that these studies were done with varying mucositis prophylaxis regimens, limiting comparisons.

The currently approved i.v. melphalan formulations, including Alkeran, contain propylene glycol, which has been associated with significant toxicities, especially when given at high doses or with prolonged exposures [30]. Although propylene glycol toxicities are usually reversible after cessation of the offending agent, they may in some cases require hemodialysis or be potentially life-threatening if not aggressively treated [12]. The concentration of propylene glycol in Alkeran for Injection (melphalan HCl) is greater than 6 g/50 mg Alkeran. Thus, high-dose (200 mg/m^2) conditioning treatment of patients with MM undergoing ASCT with Alkeran exposes patients to 24 g/m^2 of propylene glycol. When infused over 15 minutes, these patients are exposed to a propylene glycol infusion rate that is nearly 60 times faster than the recommended rate, which increases the potential for propylene glycol–associated adverse events. However, clinically significant propylene glycol–related adverse events are not generally identified in the ASCT setting.

In conclusion, this study confirmed the efficacy and safety profile of EVOMELA at a 200 mg/m^2 dose in patients undergoing upfront or salvage ASCT for MM and including patients up to 73 years of age [31]. Overall, EVOMELA was shown to be effective, inducing MM responses for all patients after successful myeloablation and subsequent engraftment (neutrophil and platelet) with no TRM. The safety profile of EVOMELA in this study was shown to be consistent with the established side effect profile of high-dose i.v. melphalan, with lower rates of grade 3 and 4 mucositis (WHO grade) or mucositis/stomatitis (NCI CTCAE grade) than has been reported in the recent literature after high-dose regimens with conventional i.v. melphalan formulations.

Use of the Captisol technology has enabled the development of propylene glycol-free melphalan HCl, which has been shown to be a more stable formulation of i.v. melphalan that does not require the propylene glycol diluent required in current i.v. melphalan formulations, including Alkeran; this new Captisol-enabled melphalan formulation is bioequivalent to Alkeran. The longer stability of EVOMELA eliminates the time constraints imposed on pharmacists and nursing staff when preparing and administering high-dose melphalan infusions, allowing for the administration of high-dose melphalan infusions for up to 8 hours after reconstitution and resulting in more reliable delivery of the planned high-dose melphalan conditioning regimen. By eliminating the propylene glycol diluent required in current melphalan formulations, EVOMELA HCl has the potential to provide a safer method of administering the high-dose melphalan conditioning regimens used in MM patients undergoing ASCT and improves the clinical administration logistics. These findings make EVOMELA an attractive alternative treatment option compared with other available i.v. melphalan formulations for use in high-dose melphalan therapy.

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REFERENCES

1. Cavo M, Rajkumar SV, Palumbo A, et al. International Myeloma Working Group consensus approach to the treatment of multiple myeloma patients who are candidates for autologous stem cell transplantation. *Blood*. 2011;117:6063-6073.
2. Shah N, Callander N, Ganguly S, et al. Hematopoietic stem cell transplantation for multiple myeloma: guidelines from the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2015;21:1155-1166.
3. Costa LJ, Huang JX, Hari PN. Disparities in utilization of autologous hematopoietic cell transplantation for treatment of multiple myeloma. *Biol Blood Marrow Transplant*. 2015;21:701-706.
4. Bensinger W. Stem-cell transplantation for multiple myeloma in the era of novel drugs. *J Clin Oncol*. 2008;26:480-492.
5. Facon T, Darre S. Frontline treatment in multiple myeloma patients not eligible for stem-cell transplantation. *Best Pract Res Clin Haematol*. 2007;20:737-746.
6. Niesvizky R, Jayabalan DS, Christos PJ, et al. BiRD (Biaxin [clarithromycin]/Revlimid [lenalidomide]/dexamethasone) combination therapy results in high complete- and overall-response rates in treatment-naive symptomatic multiple myeloma. *Blood*. 2008;111:1101-1109.
7. Moreau P, Facon T, Attal M, et al. Comparison of 200 mg/m(2) melphalan and 8 Gy total body irradiation plus 140 mg/m(2) melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myelome 9502 randomized trial. *Blood*. 2002;99:731-735.
8. Benson DM Jr, Elder PJ, Lin TS, et al. High-dose melphalan versus busulfan, cyclophosphamide, and etoposide as preparative regimens for autologous stem cell transplantation in patients with multiple myeloma. *Leuk Res*. 2007;31:1069-1075.
9. Anagnostopoulos A, Aleman A, Ayers G, et al. Comparison of high-dose melphalan with a more intensive regimen of thiotepa, busulfan, and cyclophosphamide for patients with multiple myeloma. *Cancer*. 2004;100:2607-2612.
10. Brinker BT, Waller EK, Leong T, et al. Maintenance therapy with thalidomide improves overall survival after autologous hematopoietic progenitor cell transplantation for multiple myeloma. *Cancer*. 2006;106:2171-2180.
11. *Alkeran for Injection*. Rockville, MD: Apo-Pharma USA Inc.; 2012.
12. Barnes BJ, Gerst C, Smith JR, et al. Osmol gap as a surrogate marker for serum propylene glycol concentrations in patients receiving lorazepam for sedation. *Pharmacotherapy*. 2006;26:23-33.
13. Koltun M, Morizzi J, Katneni K, et al. Preclinical comparison of intravenous melphalan pharmacokinetics administered in formulations containing either (SBE)7 m-beta-cyclodextrin or a co-solvent system. *Biopharm Drug Dispos*. 2010;31:450-454.
14. Aljitawi OS, Ganguly S, Abhyankar SH, et al. Phase IIa cross-over study of propylene glycol-free melphalan (LGD-353) and alkeran in multiple myeloma autologous transplantation. *Bone Marrow Transplant*. 2014;49:1042-1045.
15. *Vfend—voriconazole injection, powder, lyophilized, for solution*. New York, NY: Roerig, Division of Pfizer, Inc.; 2015.
16. *Nexterone—amiodarone hydrochloride injection, solution*. Deerfield, IL: Baxter Healthcare Corp.; 2015.
17. *Geodon—ziprasidone mesylate injection, powder, lyophilized, for solution. Roerig*. New York, NY: Roerig, Division of Pfizer, Inc.; 2015.
18. *Abilify*. Rockville, MD: Otsuka America Pharmaceutical, Inc.; 2014.
19. *Kyprolis—carfilzomib injection, powder, lyophilized, for solution*. South San Francisco, CA: Onyx Pharmaceuticals, Inc.; 2015.
20. *Noxafil—posaconazole suspension; posaconazole tablet, coated; posaconazole solution*. Whitehouse Station, NJ: Merck Sharp & Dohme Corp.; 2015.
21. Vesole DH, Crowley JJ, Catchatourian R, et al. High-dose melphalan with autotransplantation for refractory multiple myeloma: results of a Southwest Oncology Group phase II trial. *J Clin Oncol*. 1999;17:2173-2179.
22. Harousseau J, Moreau P. Autologous hematopoietic stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2009;360:2645-2654.
23. Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma. *N Engl J Med*. 2014;371:895-905.
24. Roussel M, Lauwers-Cances V, Robillard N, et al. Front-line transplantation program with lenalidomide, bortezomib, and dexamethasone combination as induction and consolidation followed by lenalidomide maintenance in patients with multiple myeloma: a phase II study by the Intergroupe Francophone du Myelome. *J Clin Oncol*. 2014;32:2712-2717.
25. Cook G, Williams C, Brown JM, et al. High-dose chemotherapy plus autologous stem-cell transplantation as consolidation therapy in patients with relapsed multiple myeloma after previous autologous stem-cell transplantation (NCRI Myeloma X Relapse [Intensive trial]): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2014;15:874-885.
26. Parmar SR, Bookout R, Shapiro JF, et al. Comparison of 1-day vs 2-day dosing of high-dose melphalan followed by autologous hematopoietic cell transplantation in patients with multiple myeloma. *Bone Marrow Transplant*. 2014;49:761-766.
27. Blijlevens N, Schwenkglenks M, Bacon P, et al. Prospective oral mucositis audit: oral mucositis in patients receiving high-dose melphalan or BEAM conditioning chemotherapy—European Blood and Marrow Transplantation Mucositis Advisory Group. *J Clin Oncol*. 2008;26:1519-1525.
28. Fleming S, Harrison SJ, Blombery P, et al. The choice of multiple myeloma induction therapy affects the frequency and severity of oral mucositis after melphalan-based autologous stem cell transplantation. *Clin Lymph Myel Leuk*. 2014;14:291-296.
29. Miyamoto T, Yoshimoto G, Kamimura T, et al. Combination of high-dose melphalan and bortezomib as conditioning regimen for autologous peripheral blood stem cell transplantation in multiple myeloma. *Int J Hematol*. 2013;98:337-345.
30. Zar T, Yusufzai I, Sullivan A, Graeber C. Acute kidney injury, hyperosmolality and metabolic acidosis associated with lorazepam. *Nat Clin Pract Nephrol*. 2007;3:515-520.
31. Sharma M, Zhang MJ, Zhong X, et al. Older patients with myeloma derive similar benefit from autologous transplantation. *Biol Blood Marrow Transplant*. 2014;20:1796-1803.